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Hippocampal functional connectivity is related to self-reported cognitive concerns in breast cancer patients undergoing adjuvant therapy

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A B S T R A C T

Nearly three out of four survivors experience Cancer-Related Cognitive Impairment (CRCI) for months or years following treatment. Both clinical and animal studies point to the hippocampus as a likely brain region affected in CRCI, however no previous study has investigated the functional connectivity of the hippocampus in CRCI. We compared hippocampal connectivity in cancer survivors and healthy controls and tested the relationship between functional connectivity differences and measures of objective and subjective cognition. Exploratory analysis of inflammatory markers was conducted in a small subset of participants as well. FMRI data were acquired during a memory task from 16 breast cancer survivors and 17 controls. The NIH Toolbox was used to assess cognitive performance and Neuro-QoL was used to measure self-reported cognitive concerns. Whole-brain group-level comparisons identified clusters with different connectivity to the hippocampus in survivors versus controls during task. Average connectivity was extracted from clusters of significant difference between the groups and correlated with cognitive performance and subjective report. Survivors performed worse on a test of episodic memory and reported greater cognitive concern than controls. Exploratory analysis found higher IL6 in cancer survivors compared to controls. Cancer survivors demonstrated higher connectivity of hippocampus with left cuneus, left lingual, left precuneus, and right middle prefrontal gyrus compared with controls. In survivors, higher task-related hippocampal-cortical connectivity was related to worse subjective measures of cognitive concern. Of the four significant clusters, higher connectivity of the precuneus with hippocampus was significantly associated with worse cognitive concern in survivors. The observed greater hippocampal-cortical connectivity in survivors compared to controls is the first reported fMRI biomarker of subjective concern, and may represent a compensatory response to cancer and its treatments. This compensation could explain, in part, the subjective feelings of cognitive impairment that were reported by survivors.

1. Introduction

Up to 75% of survivors experience Cancer-related Cognitive Impairment (CRCI) for months or years following treatment (Ahles et al., 2012; Janelsins et al., 2014). CRCI can have significant negative impacts on survivors, including problems with treatment adherence and decreased quality of life (Janelsins et al., 2014). Developing methods to detect and mitigate CRCI is essential to improving cancer survivors' quality of life.

Both objective and subjective cognitive impairment have been reported in survivors following cancer treatment (Biglia et al., 2012; Hurria et al., 2006; Hutchinson et al., 2012; Jenkins et al., 2006; O'Farrell et al., 2013; Scherling and Smith, 2013; Shilling and Jenkins, 2007); the most frequently impaired cognitive domains include working and long-term memory, executive functioning, processing speed and attention (Ahles et al., 2010; Bender et al., 2006; Debess et al., 2010; Hermelink et al., 2007; Janelsins et al., 2011; Wefel et al., 2010). However, most studies have found that objective cognitive deficits measured through laboratory tests did not represent and could not explain the subjective cognitive complaints reported by cancer survivors (Hutchinson et al., 2012; Jansen et al., 2011; O'Farrell et al., 2013). It would be important to understand the neural mechanisms related to CRCI, identify the neurophysiological correlates of CRCI, and develop neuroimaging biomarkers of both objective and subjective deficits in CRCI.

Chemotherapy, hormone therapy and other cancer treatments are thought to impair cognitive functioning by altering specific brain structures and/or impairing connectivity between brain regions

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(Meyers, 2008). Collectively, neuroimaging studies suggest that adjuvant cancer therapies induce dysregulations to the brain's network hubs, including the hippocampus, prefrontal cortex, and the default mode network (Bruno et al., 2012; Chen et al., 2017; de Ruiter et al., 2011; Dumas et al., 2013; Ferguson et al., 2007b; Kesler et al., 2009; Kesler et al., 2013b; Meyers, 2008). The hippocampus, which is of critical importance to memory, has been shown to be vulnerable to the effects of cancer treatments (Inagaki et al., 2007; Kesler et al., 2013a). Both human and animal studies have shown associations between chemotherapeutic treatments with common chemotherapeutics and a variety of abnormal changes to the hippocampus, including loss of gray and white matter, decreased neurogenesis, increased cell death, and blood vessel damage (Dietrich et al., 2006; Inagaki et al., 2007; Nobakht et al., 2009; Seigers et al., 2010).

Recent work by our group revealed a localized loss of hippocampal volume in breast cancer survivors undergoing adjuvant therapy as compared with healthy controls (Apple et al., 2017). Moreover, the hippocampal structural loss co-localized to a region of decreased activity in the same survivors during a covert spatial memory task using functional magnetic resonance imaging (fMRI) (Ryals et al., 2015a). Most interestingly, survivors and controls did not differ in cognitive task performance, and that none of the measures of structural loss or reduced activity were correlated with objective tests or subjective Patient Reported Outcomes (PRO) of cognition in the survivors. To gain deeper insight into a potential brain-based mechanism in the context of CRCI, we sought to explore ways in which the brain may compensate for structural and functional deficits while maintaining cognitive task performance.

In fMRI studies reported in the literature (Bruno et al., 2012; de Ruiter et al., 2011; Kesler, 2014), no increases in task-related activity has explained a compensatory response in CRCI, such as ones reported by Dickerson and colleagues in individuals with mild cognitive impairment (Dickerson et al., 2005). Functional connectivity, on the other hand, could be investigated for its potential role in compensation. Research has shown that improved cognitive performance can be attributable to increased resting-state network functional connectivity. Specifically, research on healthy adults has found a relationship between higher performance on perceptual tasks and increased functional connectivity between visual and prefrontal regions (Baldassarre et al., 2012). A study in healthy adults using noninvasive high-frequency repetitive transcranial magnetic stimulation showed improved memory was accompanied by strengthened hippocampal-cortical functional connectivity (Wang et al., 2014). In a study by Seeley and colleagues, stronger functional connectivity within the executive-control network was related to higher executive task performance in younger healthy adults (Seeley et al., 2007). Studies in aging pollutions have found increased connectivity in the default mode network in healthy older adults compared with MCI subjects (Dong et al., 2012). In the current study, we compared hippocampal functional connectivity during the covert spatial memory task (Ryals et al., 2015a) between survivors and healthy controls, and hypothesized that compensatory differences in task-based functional connectivity would be observed in survivors and they would be related to measures of objective and subject tests of cognition. Additionally, research has found an association between cytokine concentration and cognitive performance in breast cancer patients (Cheung et al., 2015). For example, increased sTNFRI and sTNFRII concentrations have been associated with poorer visual memory performance (Williams et al., 2018). To explore relationships of connectivity imaging markers with systemic inflammatory markers as a protentional mechanism for CRCI, several pro-inflammatory cytokine markers including interleukin-1 (IL-1), IL-6, and IL-10 as well as c-reactive protein (CRP) and tumor necrosis factor (TFNα) were collected and analyzed in the survivors. Relationships between elevated cytokines and measures of imaging, cognition and self-report were also explored.

2. Participants and methods

2.1. Participants

The Institutional Review Board at Northwestern University approved this study in accordance with the Declaration of Helsinki. As described in our previous paper (Apple et al., 2017), 16 pre-menopausal breast cancer survivors and 18 healthy controls gave written informed consent and were enrolled into the study. Breast cancer survivors had invasive ductal carcinoma, metastatic lobular carcinoma or inflammatory breast cancer without brain metastases, confirmed with histology. All survivors had completed systemic chemotherapy interventions within 18 months of the study, and were undergoing estrogen blockade therapy (Tamoxifen) at the time of the study. Only breast cancer survivors who scored a 0 or 1 on the physician-rated Eastern Cooperative Oncology Group (ECOG) were included in the study (0 – good functional status, 1 – symptomatic and restricted in physically strenuous activity but otherwise ambulatory, 2 – capable of all self-care but requiring rest up to half of the waking day, 3 – requiring rest more than half of the waking day, 4 – bedridden) (Oken et al., 1982). As an exploratory analysis, inflammatory markers were collected in a subset of the participants. Serum was harvested and assayed in duplicate by custom multiplex immunoassay (MesoScale Disovery V-Plex) on a SECTOR Imager 2400A (MesoScale Discovery) and IL-10 and IL-10 M450 from 11 cancer survivors and 12 controls, and IL1β, IL1β M450, IL6, IL6 M450, TNFα, TNFα M450, CRP and CRP M450 were collected from 12 participants per group.

Participants were right handed 18–45 years old, had normal or corrected vision, reported no history of current or past neurological or psychiatric disorders or psychoactive drugs at the time of the study. Of the 18 controls, one was unable to complete fMRI, and one did not complete the cognitive testing. Of the 16 survivors, one did not complete self-report questionnaires and cognitive testing. Objective cognitive performance data included 15 survivors and 17 controls, self-report data included 15 survivors and 18 controls, and fMRI data included 16 survivors and 17 controls.

2.2. Cognitive assessment

The NIH Toolbox Cognition Battery (www.nihtoolbox.org) (Weintraub et al., 2013) was administered to participants on site, consisting of seven subtests including picture Sequence Memory Test (measure of episodic memory thought to be related to hippocampal functioning (Bauer et al., 2013)), List Sorting Working Memory Test (for working memory), Flanker Inhibitory Control and Attention Test (for executive function, attention and inhibitory control), Pattern Comparison Processing Speed Test (for processing speed), and Dimensional Change Card Sort Test (for executive function and set shifting), Picture Vocabulary Test, and Oral Reading Recognition Test (for language). Raw scores on each subtest were standardized to a standardized T-scores with a normative mean of 50 and a standard Deviation of 10.

2.3. Self-report measures

Participants completed two computerized adaptive tests to assess their subjective daily function, Neuro-QoL and PROMIS pain interference. Neuro-QoL (www.neuroqol.org) reports cognitive, emotional, and functional concerns in the past week. PROMIS pain interference (www.nihpromis.org) assesses the extent to which pain effects their functioning (Cella et al., 2012). In Neuro-QoL, the Applied cognition-General Concerns subtest assesses cognitive functioning including perceived difficulties in memory, attention and decision making (e.g. “I had to read something several times to understand it,” “I had difficulty doing more than one thing at a time,” “I had trouble thinking clearly,” “My thinking was slow,” “I had trouble remembering new information, like phone numbers or simple instructions,” “I had to work really hard